

# The value of sperm DNA fragmentation testing in real-life clinical presentations

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We want to congratulate the authors for their commentary on “*clinical utility of sperm DNA fragmentation testing: practice recommendations based on clinical scenarios*”, by Agarwal *et al.* (1). The authors have given a constructive critique of our article praising its structure and writing style, though they expressed their reservation on the ability of clinical scenarios to mimic real life case presentations. After highlighting the challenges that are often faced in any medical practice when dealing with a diagnostic modality that has equivocal clinical applicability, Lynne and Brackett further pointed out some of the difficulties that are specific to sperm DNA fragmentation (SDF) testing. They expressed their concern regarding the recommendation of SDF testing for patients with lifestyle risk factors. Furthermore, they rightly questioned the clinical utility of SDF in patients with severe oligozoospermia.

We undoubtedly believe that medical practice should be individualized where treatment is tailored based on each patient’s clinical condition. Case scenarios are commonly used in literature to either report a peculiar clinical condition or, as in our case, to personalize a message through giving it a clinical perspective hoping for better comprehension. Despite the availability of numerous studies exploring the impact of SDF on male fertility and reproductive outcome, an understanding of the clinical utility of such an important test was still lacking. Therefore, in order to point out the clinical indications for SDF testing we thought of utilizing a case scenario theme with which the clinician is most familiar. The scenarios used represent cases that are commonly encountered in practice and, as perfectly enumerated by

Lynne and Brackett, indicate the use of SDF in varicocele, unexplained infertility, recurrent pregnancy loss, repeated intrauterine insemination (IUI) and *in vitro* fertilization (IVF) failure, recurrent abortion after IVF and intracytoplasmic sperm injection (ICSI) and in patients with lifestyle risk factors.

We agree with Lynne and Brackett that the clinical utility of SDF may be least convincing in patients with life style risk factors, especially when no other reversible reasons for high SDF are detected. Nonetheless, such information should provide solid grounds for implementing life style changes as well as allows for monitoring patient compliance with the prevention program. Cases with persistent elevation of SDF are generally managed individually according to their clinical presentation, but more importantly, knowledge of the SDF status would augment patient counselling and allow the clinician to provide a more realistic prognosis of each and every modality, the couple wish to pursue. The results of SDF testing have implications for men with risk factors seeking fertility, health care providers and decision makers alike. Since smoking and obesity are modifiable lifestyle factors that are particularly prevalent among infertile men (2), health programs focusing on smoking cessation and weight loss are expected to have a positive impact on semen quality and consequently male fertility.

Lynne and Brackett questioned the clinical utility of SDF in patients with severe oligozoospermia. The main difficulty here is that some testing modalities are unable to accurately assess the chromatin integrity when sperm are present in very low concentrations. However, terminal

deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), sperm chromatin dispersion test (SCD) and single cell gel electrophoresis assay (Comet) have been used to measure the degree of SDF in low sperm concentrations, including testicular specimens (3,4). When such tests are available, the recommendation is not different than what is proposed in our clinical guidelines article (1).

Regardless of whether a SDF test has been utilized, the presence of recurrent failure or miscarriage after ICSI in patients with severe oligozoospermia has raised the question of whether using testicular sperm would improve the patients' reproductive outcome (5,6). One can reasonably argue that ejaculated sperm should have a better fertilization potential than testicular sperm as they have completed their maturation during transit through the male reproductive tract (7). On the one hand, the advances in sperm preparation and selection, as well as in the techniques of ART, resulted in comparable pregnancy rates between testicular and ejaculated sperm among men with similar etiology of male infertility (8). On the other hand, recent reports suggest that low sperm quality may adversely impact ICSI outcomes (4,9-11). The reasons are not entirely understood, but it has been suggested that an underlying genetic component associated with the impaired sperm characteristics may be the leading cause of worse ICSI outcomes with the use of abnormal sperm.

Few studies have explored using testicular sperm in patients with severe oligozoospermia. Weissman *et al.* (5) reported better implantation and pregnancy rates with testicular sperm in comparison to ejaculated sperm in four patients with severe oligoasthenoteratozoospermia. Similarly, Hauser *et al.* (6) and Ben-Ami *et al.* (12) reported better implantation and pregnancy rates with testicular sperm versus ejaculated sperm in men with severe oligozoospermia or cryptozoospermia. Recently, the data from these studies were summarized in a meta-analysis, which concluded that there were no differences in ICSI pregnancy rates [relative risk (RR) 0.53, 95% CI: 0.19–1.42,  $I^2=67%$ ] or fertilization rates (RR 0.91, 95% CI: 0.78–1.06,  $I^2=73%$ ) between testicular and ejaculated sperm groups (13). The authors concluded that use of testicular sperm rather than ejaculated sperm for ICSI in men with cryptozoospermia is not recommended. However, the included studies have many limitations. Apart from being underpowered to detect clinically significant differences, only one of them have considered live birth rates as the primary outcome. Moreover, none of them have evaluated SDF levels in ejaculated or testicular specimens. Therefore, the conclusions of this meta-analysis should be taken with caution adequately powered and properly designed studies are developed.

Lastly, the studies of Mehta *et al.* (3) and Esteves *et al.* (4) provides some answers to the question raised by Lynne and Brackett regarding the use of testicular sperm in men with oligozoospermia. In the former, the authors evaluated 24 severe oligozoospermic men who failed 1 or more ART cycles using ejaculated sperm with a TUNEL-positive proportion  $>7%$  and subsequently underwent an ICSI cycle with testicular sperm. The authors reported a significantly lower TUNEL-positive rate in testicular compared with ejaculated sperm (4.6% *vs.* 24.5%). Moreover, a 50% pregnancy and live-birth rate was reported with testicular sperm in couples who had previously failed one or more IVF-ICSI cycles with ejaculated sperm (3). In the latter, the authors enrolled 172 infertile men with mild to moderate idiopathic oligozoospermia (5–15 million spermatozoa/mL) presenting with persistent high SDF ( $>30%$ ) despite oral antioxidant therapy for 3 months. The comparison groups were similar concerning male and female demographic characteristics. However, the miscarriage rates were lower whereas the live birth rates were higher in the couples subjected to sperm injections with testicular sperm. The adjusted relative risk for miscarriage and live birth between testicular and ejaculated groups were 0.29 (95% CI: 0.10–0.82;  $P=0.019$ ) and 1.76 (95% CI: 1.15–2.70;  $P=0.008$ ) respectively. To our knowledge, this is the largest study published to date comparing SDF and ICSI outcomes in couples whose male partner had elevated SDF.

Finally, as Lynne and Brackett's concluded, the intended aim from the clinical guideline article was to elucidate the clinical utility of SDF testing in a format that mimics real life experiences.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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